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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,145	06/22/2001	Seung U. Kim	UBC-002	8023

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/887,145	KIM, SEUNG U.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 June 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I (claims 1-14) in Paper No. 10 (19 March 2003) is acknowledged. Applicant's traversal is found persuasive. Group I and II are hereby rejoined and claims 1-17 are under examination.

Drawings

2. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: the components of Figures 2, 3, 4, and 6 are not explained in the specification. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

3. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: Figure 6 contains five components (A-E). A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Sequence Rules

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However,

this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below. This application discloses a nucleic acid sequences on pp. 27-29 and an amino acid sequence on pp. 31 line 4. These sequences must be assigned SEQ ID NO's. Correction is required.

Claim Objections

5. Claims **12, 13**, and **14** are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 12, 13, and 14 are drawn to intended uses of the microglial cell line and therefore fail to further limit the product of claim 1.

Double Patenting

Non-Statutory Obvious-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims **14-17** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim **4** of copending Application No. 09/855468. Although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims describe the use of an amphotrophic replication-incompetent retroviral vector encoding *v-myc* oncogene to transfect human microglial cells to make an immortalized cell line.

7. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Claims **1-13** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-3** of copending Application No. 09/855468. Although the conflicting claims are not identical, they are not patentably distinct from each other because all the claims are drawn to an immortalized human cell line with the characteristics of human microglia.

9. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims **1-14** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The invention appears to be a novel cell line (i.e., HM06). Since the HM06 (material in question) are essential to the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the cell lines are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the nucleic acid molecules. The specification does not disclose a repeatable process to obtain the cell lines and it is not apparent if the cell lines are readily available to the public.

11. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific nucleic acid molecules have been deposited under the Budapest Treaty and that the cell line (HM06) will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

12. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

13. Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include such, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information. Finally, Applicant is advised that the address for the ATCC has recently changed, and that the new address should appear in the specification. The new address is:

American Type Culture Collection

10801 University Boulevard

Manassas, VA 20110-2209

14. Furthermore, claims **1-14** are enabled for not enabled *for any microglia cell line other than a genetically modified microglia cell line*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

15. The above invention is drawn to a microglia cell line with intended uses of screening, treatments for neurodegenerative disease, and treatments of pathologies. The language of said claims encompasses both *in vivo* and *in vitro* activity. The specification teaches a method of isolating and genetically modifying the cells *in vitro*. However, no reproducible method of making a microglial cell line with all the characteristics as defined by claims 1-12 is presented.

16. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods. Additionally, a person skilled in the art would recognize that predicting the efficacy of microglia cell line based solely on the isolation of a single cell line is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of making the claimed cells, such a disclosure would not be considered enabling since the state of genetically modified microglia cell lines is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

17. The following references are cited herein to illustrate the state of the art of microglia cell lines.

18. Hosaka *et al.* (20 July 1992) "Generation of microglial cell lines by transfection with simian virus 40 large T gene." Neuroscience Letters **141**(2): 139-142 teaches that the transfection of microglial cultures with an oncogene, such as the large T antigen, leads to numerous clones which vary in phenotype (pp. 139-140). This requires isolation of suitable tissue, transfection with an oncogene, selection with a selectable marker (such as neo^R), and then subsequent screening to identify the characteristics of the cell line (pp. 139-140). Of the 52 clones isolated by Hosaka *et al.*, only one was selected for further characterization (pp. 140). Thus a skilled artisan is presented with a large burden of experimentation, with a unpredictable outcome to practice the invention as claimed.

19. Said claims are also drawn very broadly to methods of treating any condition or disease suspected of being associated with microglia in humans. Since the specification fails to provide any guidance for the successful treatment or prevention of such a broad range of diseases, and since resolution of the various complications in regards to targeting a particular cell or cellular deficiency in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and /or tissues. In the absence of any

real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims **15-17** are rejected under 35 U.S.C. 103(a) as being unpatentable over Janabi *et al.* (16 August 1996) "Establishment of human microglial cell lines after transfection of primary cultures of embryonic microglial cells with the SV40 large T antigen." Neuroscience Letters **195**(2): 105-108 and Briers *et al.* (July 1994) "Generation and characterization of mouse microglial cell lines." Journal of Neuroimmunology **52**(2): 153-164 in view of **US 5762926** (9 July 1998) Gage *et al.*

21. Janabi *et al.* teaches the isolation, culturing, and transfection with a large T antigen of human microglial cells to produce an immortalized (and hence genetically modified) cell line (pp. 105-106). Janabi *et al.* does not teach, however, the use of a *v-myc* oncogene or a replication-deficient (or replication-incompetent) retroviral vector.

22. Briers *et al.* the isolation, culturing, and transfection of a murine microglial cell line using *v-myc* gene (pp. 153-154; "2.1 Cell cultures").

23. US 5762926 teaches a method using replication-defective retroviruses to transfect human cells to make immortalized cell lines (Col. 4 lines 11-50; Col. Lines 36-49; claim 51).

24. Thus, it would have been obvious to a person of ordinary skill in the art at the time of the invention to combine the method of immortalizing microglial cells with a *v-myc* oncogene as taught by Briers *et al.* in a replication-deficient retroviral vector as taught by US 5762926 on human microglial cells as taught by Janabi *et al.*

25. A person of ordinary skill in the art at the time of the invention would have been motivated to make these modifications because the danger associated with the secretion of oncogenic viruses, hence the use of replication-deficient viruses (US 5762926). Further, Briers *et al.* teaches that large T antigen can change the phenotype of the transfected cells making the *v-myc* gene a preferred oncogene (pp. 153). Another motivation would have been the advantages of the retroviral system for transfection as taught by US 5762926 including but no limited to extremely efficient in a wide range of cells, a large capacity for exogenous DNA, and little or no metabolic or genetic damage to the recipient cells (Col. 4 lines 11-23).

26. A person of ordinary skill in the art at the time of the invention would have a reasonable expectation of success in making the above mentioned modifications because Briers *et al.* demonstrated the use of *v-myc* to immortalize microglial cells and US 5762926 demonstrates that replication-deficient retroviruses can be used successfully on a wide range of cells (pp. 206; Col. 4 lines 11-23).

27. Thus the invention as a whole was *prima facia* obvious over the prior art.

Summary

28. Claims 1-17 are hereby rejected.

29. It is noted that Fontijn et al. (19 January 1999) "Maintenance of Vascular Endothelial Cell-Specific Properties after Immortalization with an Amphotrophic Replication-Deficient Retrovirus Containing Human Papilloma Virus 16 E6/E7 DNA." Experimental Cell Research **216**(1): 199-207 teaches that amphotrophic viruses are used to transfect human cells. Therefore, any replication-decificient retroviral vector used by US 5762926 would be, by definition, amphotrophic. Fontijn *et al.* teaches the use of an amphotrophic replication-deficient retrovirus to transform human cells to make a genetically modified cell line (pp. 199-201).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
May 19, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER